

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

Date of mailing (day/month/year) 31 May 2001 (31.05.01)	To:  Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE  in its capacity as elected Office
International application No. PCT/EP00/09722	Applicant's or agent's file reference PI3806
International filing date (day/month/year) 05 October 2000 (05.10.00)	Priority date (day/month/year) 07 October 1999 (07.10.99)
Applicant  ALVARO, Giuseppe et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:  
17 April 2001 (17.04.01)

in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election  was  
 was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Cécile Chatel (Fax 338.87.40)  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)Date of mailing (day/month/year)  
07 February 2002 (07.02.02)Applicant's or agent's file reference  
PI3806International application No.  
PCT/EP00/09722

From the INTERNATIONAL BUREAU

To:

FILLER, Wendy, Anne  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 (CN9.25.1)  
 980 Great West Road  
 Brentford  
 Middlesex TW8 9GS  
 ROYAUME-UNI

## IMPORTANT NOTIFICATION

International filing date (day/month/year)  
05 October 2000 (05.10.00)

1. The following indications appeared on record concerning:

the applicant     the inventor     the agent     the common representative

## Name and Address

FILLER, Wendy, Anne  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 Two New Horizons Court  
 Brentford, Middlesex TW8 9EP  
 United Kingdom

State of Nationality	State of Residence
Telephone No. 020 8966 8412	
Facsimile No. 020 8966 8838	
Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person     the name     the address     the nationality     the residence

## Name and Address

FILLER, Wendy, Anne  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 (CN9.25.1)  
 980 Great West Road  
 Brentford  
 Middlesex TW8 9GS  
 United Kingdom

State of Nationality	State of Residence
Telephone No. +44 20 8047 5000	
Facsimile No. +44 20 8047 6894	
Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

Authorized officer

Jean-Luc MARTIN  
 Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:  
 GLAXO WELLCOME PLC  
 Glaxo Wellcome House  
 Attn. Filler, Wendy Anne  
 Berkeley Avenue  
 Greenford  
 Middlesex UB6 0NN  
 UNITED KINGDOM

Global	RECEIVED
	23 APR 2001
ACTION	DATE
SIGN	20/04/2001

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference  
**PI3806**

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.  
**PCT/EP 00/09722**International filing date  
(day/month/year)  
**05/10/2000**

Applicant

**GLAXO GROUP LIMITED et al.**

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**  
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  
  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL-2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

Authorized officer

**John De Bruijn**

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:  
 GLAXO WELLCOME PLC  
 Glaxo Wellcome House  
 Attn. Filler, Wendy Anne  
 Berkeley Avenue  
 Greenford  
 Middlesex UB6 0NN  
 UNITED KINGDOM

Global I.	
RECEIVED	23 APR 2001
ACTION DATE	O.P.K.
Date of mailing (day/month/year) <i>DM</i>	
20/04/2001	

NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT  
 OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference  
**PI3806**

**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.  
**PCT/EP 00/ 09722**

International filing date  
*(day/month/year)* **05/10/2000**

Applicant

**GLAXO GROUP LIMITED et al.**

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Name and mailing address of the International Searching Authority  
  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL-2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

Authorized officer

**John De Bruijn**

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## NOTES TO FORM PCT/ISA/220 (cont'd)

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For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  PI3806	<b>FOR FURTHER ACTION</b>	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No.  PCT/EP 00/09722	International filing date (day/month/year)  05/10/2000	(Earliest) Priority Date (day/month/year)  07/10/1999

Applicant

GLAXO GROUP LIMITED et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

## 4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

PIPERAZINE COMPOUNDS

## 5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09722

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K. BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35 ---	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D -----	1,15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

4 April 2001

20/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/09722

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09722

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 4308387	A	29-12-1981	AT 380685 B	25-06-1986
			AT 219383 A	15-11-1985
			AT 376666 B	27-12-1984
			AT 683479 A	15-05-1984
			AU 529260 B	02-06-1983
			AU 5198479 A	19-06-1980
			BE 879528 A	21-04-1980
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EPA EPO-OEB	
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Reçu:	
05.10.2000	
11	ANL ZEICHN.

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**PCT REQUEST**

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

PI3806

0	For receiving Office us only International Application No.	<b>PCT/EP 00 / 09722</b>
0-1		
0-2	International Filing Date	<b>05 OCT 2000 (05.10.00)</b>
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.91 (updated 01.07.2000)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	PI3806
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant II-1 This person is: II-2 Applicant for II-4 Name II-5 Address:	applicant only all designated States except US GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD, Middlesex UB6 0NN United Kingdom
II-6	State of nationality	GB
II-7	State of residence	GB
II-8	Telephone No.	020 8966 8000
II-9	Facsimile No.	020 8966 8838
III-1	Applicant and/or inventor III-1-1 This person is: III-1-2 Applicant for III-1-4 Name (LAST, First) III-1-5 Address:	applicant and inventor US only ALVARO, Giuseppe Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-1-6	State of nationality	IT
III-1-7	State of residence	IT

## PCT REQUEST

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

III-2	Applicant and/or inventor This person is:	applicant and inventor
III-2-1		US only
III-2-2	Applicant for	
III-2-4	Name (LAST, First)	DI FABIO, Romano
III-2-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-2-6	State of nationality	IT
III-2-7	State of residence	IT
III-3	Applicant and/or inventor This person is:	applicant and inventor
III-3-1		US only
III-3-2	Applicant for	
III-3-4	Name (LAST, First)	GIOVANNINI, Riccardo
III-3-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-3-6	State of nationality	IT
III-3-7	State of residence	IT
III-4	Applicant and/or inventor This person is:	applicant and inventor
III-4-1		US only
III-4-2	Applicant for	
III-4-4	Name (LAST, First)	GUERCIO, Giuseppe
III-4-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-4-6	State of nationality	IT
III-4-7	State of residence	IT
III-5	Applicant and/or inventor This person is:	applicant and inventor
III-5-1		US only
III-5-2	Applicant for	
III-5-4	Name (LAST, First)	ST-DENIS, Yves
III-5-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-5-6	State of nationality	CA
III-5-7	State of residence	IT

## PCT REQUEST

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

III-6	Applicant and inventor This person is:	applicant and inventor
III-6-1		US only
III-6-2	Applicant for	URSINI, Antonella
III-6-4	Name (LAST, First)	Glaxo Wellcome SpA
III-6-5	Address:	Via Alessandro Fleming 2
		I-37135 Verona
		Italy
III-6-6	State of nationality	IT
III-6-7	State of residence	IT
IV-1	Agent or common representative; or address for correspondence  The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	FILLER, Wendy, Anne
IV-1-2	Address:	Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom
IV-1-3	Telephone No.	020 8966 8000
IV-1-4	Facsimile No.	020 8966 8838
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<p>AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT</p> <p>EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT</p> <p>EP: AT BE CH&amp;LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE, and any other State which is a Contracting State of the European Patent Convention and of the PCT</p> <p>OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT</p>
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<p>AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&amp;LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW</p>

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## PCT REQUEST

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

V-5	<b>Precautionary Designation Statement</b> In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	<b>Exclusion(s) from precautionary designations</b>		
VI-1	<b>Priority claim of earlier national application</b>		
VI-1-1	Filing date	07 October 1999 (07.10.1999)	
VI-1-2	Number	9923748.9	
VI-1-3	Country	GB	
VII-1	<b>International Searching Authority Chosen</b>		
<b>European Patent Office (EPO) (ISA/EP)</b>			
VIII	<b>Check list</b>		
VIII-1	Request	number of sheets	electronic file(s) attached
VIII-2	Description	5	-
VIII-3	Claims	96	-
VIII-4	Abstract	6	-
VIII-5	Drawings	2	pi3806-cab.txt
VIII-7	<b>TOTAL</b>	0	-
VIII-8	<b>Accompanying items</b>	109	-
VIII-9	Fee calculation sheet	✓	-
VIII-12	Separate signed power of attorney	✓	-
VIII-16	Priority document(s)	Item(s) VI-1	-
VIII-18	PCT-EASY diskette	-	diskette
VIII-19	Figure of the drawings which should accompany the abstract		
IX-1	Language of filing of the international application	English	
IX-1-1	Signature of applicant or agent		
IX-1-1	Name (LAST, First)	FILLER, Wendy, Anne	

## FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	05 OCT 2000 (05.10.00)
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	

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**PCT REQUEST**

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

**FOR INTERNATIONAL BUREAU USE ONLY**

11-1	Date of receipt of the record copy by the International Bureau	
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PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

Filler, Wendy Anne  
GLAXO WELLCOME PLC  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
GRANDE BRETAGNE

NOTIFICATION OF THE INTERNATIONAL  
APPLICATION NUMBER AND OF THE  
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing  
(day/month/year)

07 11 2000

Applicant's or agent's file reference  
PI3806

IMPORTANT NOTIFICATION

International application No.  
PCT/EP 00/09722

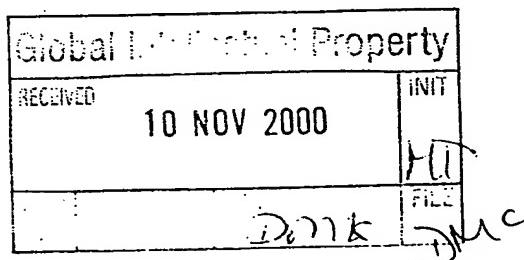
International filing date (day/month/year)  
05/10/2000

Priority date (day/month/year)  
07/10/1999

Applicant  
GLAXO GROUP LIMITED

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.
3.  Other:



- \* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office  
  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL-2280 HV Rijswijk  
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+ 31-70) 340-3016

Authorized officer

R.L.R. PETHER

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Filler, Wendy Anne  
GLAXO WELLCOME PLC  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
GRANDE BRETAGNE

CORPORATE INTELLECTUAL PROPERTY	
Received 15 GEN 2002	
VERONA	File PCT

Corporate Intellectual Property		NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)	
RECEIVED		INIT	
- 7 JAN 2002			
Action Date	FILE	Date of mailing (day/month/year) 03.01.2002	

Applicant's or agent's file reference  
PI3806

## IMPORTANT NOTIFICATION

International application No. PCT/EP00/09722	International filing date (day/month/year) 05/10/2000	Priority date (day/month/year) 07/10/1999
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Applicant  
GLAXO GROUP LIMITED et al.

09 JAN 2002

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel. +49 89 2399-8012



**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**  
**(PCT Article 36 and Rule 70)**

Applicant's or agent's file reference  PI3806	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/EP00/09722	International filing date (day/month/year)  05/10/2000	Priority date (day/month/year)  07/10/1999	
International Patent Classification (IPC) or national classification and IPC  C07D241/04			
<p><b>Applicant</b>  <b>GLAXO GROUP LIMITED et al.</b></p>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II    <input type="checkbox"/> Priority</li> <li>III    <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV    <input type="checkbox"/> Lack of unity of invention</li> <li>V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI    <input type="checkbox"/> Certain documents cited</li> <li>VII    <input type="checkbox"/> Certain defects in the international application</li> <li>VIII    <input type="checkbox"/> Certain observations on the international application</li> </ul>			
Date of submission of the demand  17/04/2001	Date of completion of this report  03.01.2002		
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Schuemacher, A Telephone No. +49 89 2399 7818		



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

**I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-96                   as originally filed

**Claims, No.:**

1-19                   as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,       pages:
- the claims,           Nos.:
- the drawings,       sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- the entire international application.
- claims Nos. 18.

because:

- the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-19
Inventive step (IS)	Yes: Claims
	No: Claims 1-19
Industrial applicability (IA)	Yes: Claims 1-17, 19

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

No: Claims

2. Citations and explanations  
see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1:US-A-4 308 387 (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29)

D2:DAVID T. DAVIES: 'SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES' JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820

Reference is also made to the letter of the Applicant dated the 1<sup>st</sup> of November 2001 and to document D3:

D3: WO 97/36593 A (MERCK & Co.) 9 October 1997

**1. Novelty, Article 33(2) PCT:**

The present application discloses piperazine compounds, which are potent and specific antagonists of tachykinins, processes for their preparation and the pharmaceutical compositions containing them.

Document D1 describes diphenylbutyl-piperazinecarboxamides, from which the subject-matter of claim 1 differs mainly in that the substituent R<sub>4</sub> in formula (I) cannot be a diphenylbutyl-substituent.

Document D2 discloses piperazine-2,3-diones, which differ from the compounds of claim 1 because of the presence of the carbonyl group in position 3.

The Applicant cites document 3 in which inhibitors of farnesyl-protein transferase are disclosed. These compounds can have the same formula as the present claimed compounds (see in D3, claim1, W is a heterocycle, p=0, X is CO, s is 0, G is H<sub>2</sub> and R<sup>2</sup> or R<sup>3</sup> can be an aryl ring substituted with one or more fluorine). Even if the Applicant has disclaimed these particular compounds (when R<sup>1</sup> and R<sup>2</sup> form a heterocycle, then m is 1 or 2 and R is not fluorine) he should also disclaim in order to meet the requirements for novelty the case, when R<sup>1</sup> and R<sup>2</sup> form a heterocycle and m is 3, then R must not be fluorine, otherwise the subject-matter of claim 1-17 and 19 can not be considered as new (Art. 33(2), PCT).

**2. Inventive step, Article 33(3) PCT:**

The problem to be solved by the present invention may be regarded as to find piperazine derivatives, which are potent and specific antagonists of tachykinins.

The document D1 is regarded as being the closest prior art to the subject-matter of the present application, and shows diphenylbutyl-piperazinecarboxamides, which differ from the compounds of claim 1 because of the diphenylbutyl-substituent on the nitrogen atom of the piperazine ring.

The examining division agrees with the Applicant, that there is no prediction or suggestion in D1, that this diphenylbutyl substituent borne by the nitrogen-atom of the piperazine ring could be interchanged with other substituent defined as R<sub>4</sub> in the present application; therefore the subject-matter of claim 1 could be regarded as involving an inventive step.

However, It should be pointed out that it must be made credible that essentially all of the claimed matter solves the given problem and that only the compounds which are suitable for solving the problem underlying the present subject-matter could be claimed.

Now in the description, the compounds tested for their affinity for NK1 receptor are those where R<sub>4</sub> is almost always hydrogen, R<sub>5</sub> is always methyl or hydrogen and R<sub>3</sub> is always CF<sub>3</sub> (n=2) and therefore, the scope of the claim 1 seems to be too broad and not supported by the description.

Consequently, claim 1 as well as dependant compounds-claims 2-15, claims 16 and 17 concerning the use and the pharmaceutical composition containing such compounds and the process for their preparation disclosed in claim 19 do not meet the requirements of

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/09722

Article 33(2) and 33(3) PCT.

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 12 April 2001 (12.04.01)	To: FILLER, Wendy, Anne Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN ROYAUME-UNI [REDACTED] Actual Proprietary 20 APR 2001 [Signature]	
Applicant's or agent's file reference PI3806 /PCT	DNC DMC <b>IMPORTANT NOTICE</b>	
International application No. PCT/EP00/09722	International filing date (day/month/year) 05 October 2000 (05.10.00)	Priority date (day/month/year) 07 October 1999 (07.10.99)
Applicant GLAXO GROUP LIMITED et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,  
FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,  
MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,  
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
12 April 2001 (12.04.01) under No. WO 01/25219

**REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)**

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))**

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.83.38
--	---

INTERNATIONAL COOPERATION TREATY  
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PCT

20 AUG 2001 From the INTERNATIONAL BUREAU

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TO: PCT

Corporate Intellectual Property

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INIT

FILLER, Wendy, Anne  
GlaxoSmithKline

20 AUG 2001

Corporate Intellectual Property

Two New Horizons Court

Brentford, Middlesex TW8 9EP

ROYAUME-UNI

FILE

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year)

08 August 2001 (08.08.01)

Applicant's or agent's file reference

PI3806 /PCT

## IMPORTANT NOTIFICATION

International application No.

PCT/EP00/09722

International filing date (day/month/year)

05 October 2000 (05.10.00)

## 1. The following indications appeared on record concerning:

 the applicant the inventor the agent the common representative

## Name and Address

FILLER, Wendy, Anne  
Glaxo Wellcome plc  
Glaxo Wellcome House  
Berkeley Avenue  
Greenford, Middlesex UB6 0NN  
United Kingdom

## State of Nationality

## State of Residence

## Telephone No.

020 8966 8000

## Facsimile No.

020 8966 8838

## Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

 the person the name the address the nationality the residence

## Name and Address

FILLER, Wendy, Anne  
GlaxoSmithKline  
Corporate Intellectual Property  
Two New Horizons Court  
Brentford, Middlesex TW8 9EP  
United Kingdom

## State of Nationality

## State of Residence

## Telephone No.

020 8966 8412

## Facsimile No.

020 8966 8838

## Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

 the receiving Office the designated Offices concerned the International Searching Authority the elected Offices concerned the International Preliminary Examining Authority other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

A. Karkachi

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004199348

RECD 07 JAN 2002

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

12

Applicant's or agent's file reference PI3806	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/09722	International filing date (day/month/year) 05/10/2000	Priority date (day/month/year) 07/10/1999
International Patent Classification (IPC) or national classification and IPC C07D241/04		
<p>Applicant GLAXO GROUP LIMITED et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II    <input type="checkbox"/> Priority</li> <li>III    <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV    <input type="checkbox"/> Lack of unity of invention</li> <li>V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI    <input type="checkbox"/> Certain documents cited</li> <li>VII    <input type="checkbox"/> Certain defects in the international application</li> <li>VIII    <input type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand 17/04/2001	Date of completion of this report 03.01.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schuemacher, A Telephone No. +49 89 2399 7818



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-96                   as originally filed

**Claims, No.:**

1-19                   as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
  - the language of publication of the international application (under Rule 48.3(b)).
  - the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of: ←
- the description,       pages:
  - the claims,           Nos.:
  - the drawings,       sheets:
5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- the entire international application.
- claims Nos. 18.

because:

- the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-19
Inventive step (IS)	Yes: Claims
	No: Claims 1-19

Industrial applicability (IA) Yes: Claims 1-17, 19

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/09722

No: Claims

2. Citations and explanations  
see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1:US-A-4 308 387 (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29)

D2:DAVID T. DAVIES: 'SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES' JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820

Reference is also made to the letter of the Applicant dated the 1<sup>st</sup> of November 2001 and to document D3:

D3: WO 97/36593 A (MERCK & Co.) 9 October 1997

**1. Novelty, Article 33(2) PCT:**

The present application discloses piperazine compounds, which are potent and specific antagonists of tachykinins, processes for their preparation and the pharmaceutical compositions containing them.

Document D1 describes diphenylbutyl-piperazinecarboxamides, from which the subject-matter of claim 1 differs mainly in that the substituent R<sub>4</sub> in formula (I) cannot be a diphenylbutyl-substituent.

Document D2 discloses piperazine-2,3-diones, which differ from the compounds of claim 1 because of the presence of the carbonyl group in position 3.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

The Applicant cites document 3 in which inhibitors of farnesyl-protein transferase are disclosed. These compounds can have the same formula as the present claimed compounds (see in D3, claim1, W is a heterocycle, p=0, X is CO, s is 0, G is H<sub>2</sub> and R<sup>2</sup> or R<sup>3</sup> can be an aryl ring substituted with one or more fluorine). Even if the Applicant has disclaimed these particular compounds (when R<sup>1</sup> and R<sup>2</sup> form a heterocycle, then m is 1 or 2 and R is not fluorine) he should also disclaim in order to meet the requirements for novelty the case, when R<sup>1</sup> and R<sup>2</sup> form a heterocycle and m is 3, then R must not be fluorine, otherwise the subject-matter of claim 1-17 and 19 can not be considered as new (Art. 33(2), PCT).

**2. Inventive step, Article 33(3) PCT:**

The problem to be solved by the present invention may be regarded as to find piperazine derivatives, which are potent and specific antagonists of tachykinins.

The document D1 is regarded as being the closest prior art to the subject-matter of the present application, and shows diphenylbutyl-piperazinecarboxamides, which differ from the compounds of claim 1 because of the diphenylbutyl-substituent on the nitrogen atom of the piperazine ring.

The examining division agrees with the Applicant, that there is no prediction or suggestion in D1, that this diphenylbutyl substituent borne by the nitrogen-atom of the piperazine ring could be interchanged with other substituent defined as R<sub>4</sub> in the present application; therefore the subject-matter of claim 1 could be regarded as involving an inventive step.

However, It should be pointed out that it must be made credible that essentially all of the claimed matter solves the given problem and that only the compounds which are suitable for solving the problem underlying the present subject-matter could be claimed.

Now in the description, the compounds tested for their affinity for NK1 receptor are those where R<sub>4</sub> is almost always hydrogen, R<sub>5</sub> is always methyl or hydrogen and R<sub>3</sub> is always CF<sub>3</sub> (n=2) and therefore, the scope of the claim 1 seems to be too broad and not supported by the description.

Consequently, claim 1 as well as dependant compounds-claims 2-15, claims 16 and 17 concerning the use and the pharmaceutical composition containing such compounds and the process for their preparation disclosed in claim 19 do not meet the requirements of

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

Article 33(2) and 33(3) PCT.

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number  
**WO 01/25219 A2**(51) International Patent Classification<sup>7</sup>: C07D 241/04,  
A61K 31/496, A61P 25/22[IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2,  
I-37135 Verona (IT).

(21) International Application Number: PCT/EP00/09722

(74) Agent: FILLER, Wendy, Anne; Glaxo Wellcome plc,  
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Middlesex UB6 0NN (GB).

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language:

English

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(26) Publication Language:

English

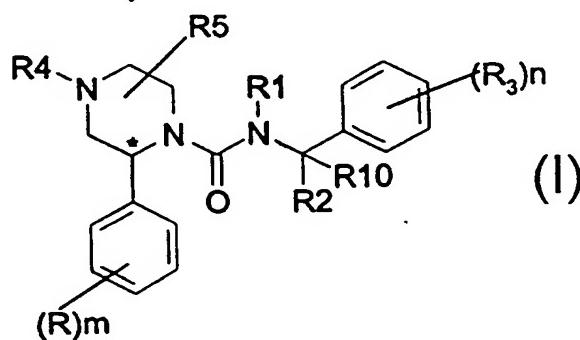
(30) Priority Data:  
9923748.9 7 October 1999 (07.10.1999) GB(71) Applicant (for all designated States except US): GLAXO  
GROUP LIMITED [GB/GB]; Glaxo Wellcome House,  
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ALVARO, Giuseppe  
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Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona  
(IT). GIOVANNINI, Riccardo [IT/IT]; Glaxo Wellcome  
SpA, Via Alessandro Fleming 2, I-37135 Verona (IT).  
GUERCIO, Giuseppe [IT/IT]; Glaxo Wellcome SpA, Via  
Alessandro Fleming 2, I-37135 Verona (IT). ST-DENIS,  
Yves [CA/IT]; Glaxo Wellcome SpA, Via Alessandro  
Fleming 2, I-37135 Verona (IT). URISINI, Antonella**Published:**— Without international search report and to be republished  
upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS



WO 01/25219 A2

hydroxy or NR<sub>8</sub>R<sub>9</sub>, wherein R<sub>8</sub> and R<sub>9</sub> represent independently hydrogen or C<sub>1-4</sub> alkyl optionally substituted by hydroxy, or by amino; R<sub>10</sub> represents hydrogen, a C<sub>1-4</sub> alkyl group or R<sub>10</sub> together with R<sub>2</sub> represents a C<sub>3-7</sub> cycloalkyl group; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that, when R<sub>1</sub> and R<sub>2</sub> together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine, and pharmaceutically acceptable salts and solvates thereof.

**(57) Abstract:** The present invention relates to piperazine derivatives of formula (I) wherein R represents a halogen atom or a C<sub>1-4</sub> alkyl group; R<sub>1</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group; R<sub>2</sub> represents hydrogen, a C<sub>1-4</sub> alkyl, C<sub>2-6</sub> alkenyl or a C<sub>3-7</sub> cycloalkyl group; or R<sub>1</sub> and R<sub>2</sub> together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group; R<sub>3</sub> represents a trifluoromethyl, a C<sub>1-4</sub> alkyl, a C<sub>1-4</sub> alkoxy, a trifluoromethoxy or a halogen group; R<sub>4</sub> represents hydrogen, a (CH<sub>2</sub>)<sub>q</sub>R<sub>7</sub> or a (CH<sub>2</sub>)<sub>r</sub>CO(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub> group; R<sub>5</sub> represents hydrogen, a C<sub>1-4</sub> alkyl or a COR<sub>6</sub> group; R<sub>6</sub> represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms; R<sub>7</sub> represents hydrogen,

## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PI3806</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/09722</b>	International filing date (day/month/year) <b>05/10/2000</b>	(Earliest) Priority Date (day/month/year) <b>07/10/1999</b>
Applicant <b>GLAXO GROUP LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

- the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

PIPERAZINE COMPOUNDS

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

EP 00/09722

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K. BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35 -----	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D -----	1,15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## ° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

4 April 2001

Date of mailing of the international search report

20/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

Authorized officer

Francois, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 00/09722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4308387	A 29-12-1981	AT 380685 B AT 219383 A AT 376666 B AT 683479 A AU 529260 B AU 5198479 A BE 879528 A CA 1130807 A CH 643247 A DE 2941880 A DK 442779 A, B, ES 485188 A FI 793238 A, B, FR 2439187 A GB 2037745 A, B HK 57184 A IT 1207269 B JP 1482061 C JP 55057572 A JP 63026756 B LU 81807 A NL 7907741 A, B, NO 793315 A, B, NZ 191867 A SE 448730 B SE 7908701 A SG 7384 G US 4385057 A US 4447433 A	25-06-1986 15-11-1985 27-12-1984 15-05-1984 02-06-1983 19-06-1980 21-04-1980 31-08-1982 30-05-1984 30-04-1980 21-04-1980 16-05-1980 21-04-1980 16-05-1980 16-07-1980 03-08-1984 17-05-1989 27-02-1989 28-04-1980 31-05-1988 25-01-1980 22-04-1980 22-04-1980 14-06-1983 16-03-1987 21-04-1980 08-02-1985 24-05-1983 08-05-1984

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number  
**WO 01/25219 A3**(51) International Patent Classification<sup>7</sup>: **C07D 241/04.**  
A61K 31/496, A61P 25/22, C07D 401/06, 403/06[IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2,  
I-37135 Verona (IT).(21) International Application Number: **PCT/EP00/09722**(74) Agent: **FILLER, Wendy, Anne**; GlaxoSmithKline,  
Corporate Intellectual Property, Two New Horizons Court,  
Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date: 5 October 2000 (05.10.2000)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

**Published:**

— with international search report

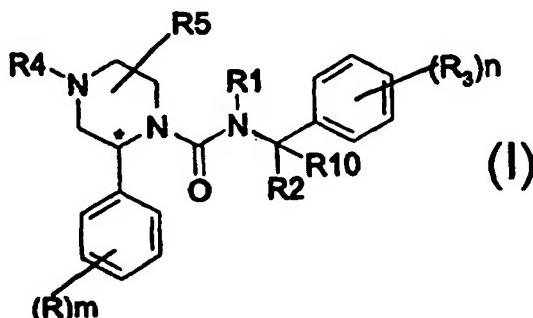
(71) Applicant (*for all designated States except US*): **GLAXO**  
**GROUP LIMITED [GB/GB]**; Glaxo Wellcome House,  
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).(88) Date of publication of the international search report:  
13 December 2001

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERAZINE COMPOUNDS

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3 nitrogen atoms; R<sub>7</sub> represents hydrogen, hydroxy or NR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub> represent independently hydrogen or C<sub>1-4</sub> alkyl optionally substituted by hydroxy, or by amino; R<sub>10</sub> represents hydrogen, a C<sub>1-4</sub> alkyl I group or R<sub>10</sub> together with R<sub>2</sub> represents a C<sub>3-7</sub> cycloalkyl group; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that, when R<sub>1</sub> and R<sub>2</sub> together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine, and pharmaceutically acceptable salts and solvates thereof.

(57) Abstract: The present invention relates to piperazine derivatives of formula (I) wherein R represents a halogen atom or a C<sub>1-4</sub> alkyl group; R<sub>1</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group; R<sub>2</sub> represents hydrogen, a C<sub>1-4</sub> alkyl, C<sub>2-6</sub> alkenyl or a C<sub>3-7</sub> cycloalkyl group; or R<sub>1</sub> and R<sub>2</sub> together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group; R<sub>3</sub> represents a trifluoromethyl, a C<sub>1-4</sub> alkyl, a C<sub>1-4</sub> alkoxy, a trifluoromethoxy or a halogen group; R<sub>4</sub> represents hydrogen, a (CH<sub>2</sub>)<sub>p</sub>R, or a (CH<sub>2</sub>)<sub>q</sub>CO(CH<sub>2</sub>)<sub>p</sub>R<sub>7</sub> group; R<sub>5</sub> represents hydrogen, a C<sub>1-4</sub> alkyl or a COR<sub>6</sub> group; R<sub>6</sub> represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09722

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K. BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35 ---	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D	1,15

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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